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Review Article

Risks and benefits of asthma therapies

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Abstract

Maintenance use of short-acting adrenergic agents can cause tachyphylaxis, increased non-specific bronchial hyperreactivity, poorer clinical control, a worsened late allergic reaction and possibly an increased risk of death; therefore, 'as needed' use is preferable. The choice of a first line anti-inflammatory drug, between inhaled corticosteroids and non-steroidal drugs (cromolyn sodium or nedocromil sodium), has to be made considering their risk–benefit ratio. Although in severe patients the efficacy of inhaled corticosteroids is clearly superior to that of cromolyn, in mild-to-moderate patients the efficacy is comparable. In terms of safety, non-steroidal drugs have a better safety profile than inhaled corticosteroids, which can cause growth suppression even at regular doses, especially in mild-to-moderate patients. Although some investigators have raised the possibility of irreversible airway obstruction if treatment with inhaled corticosteroids is delayed, studies by my group and others, using non-steroidal drugs as first line, have not confirmed that suspicion. In conclusion, a step-wise approach in children is still justified, starting with non-steroidal drugs (cromolyn sodium or nedocromil sodium) in mild persistent asthma and using inhaled corticosteroids only in patients poorly controlled by the non-steroidal drugs.

Key words: cromolyn sodium, inhaled corticosteroids, maintenance adrenergic agents, nedocromil sodium, non-steroidal anti-inflammatory drugs.

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Introduction

Risk/benefit ratios are an important consideration for every drug. For some drugs used to treat asthma, this ratio is still very much debated. Short-acting beta-adrenoreceptor agonists are the most widely used drugs in asthma and the most valuable tools for treating acute attacks. The dispute is whether they should be used as regular (maintenance) therapy or on an 'as needed' basis for symptom relief.

The other major debate is whether inhaled corticosteroids or non-steroidal, anti-inflammatory drugs, such as disodium cromoglycate (DSCG), should be the first-line anti-inflammatory treatment. This question is especially debated for children, in whom growth suppression is a potential side-effect of inhaled corticosteroids.

Maintenance adrenergic agents

Some of the evidence that regular use of adrenergic agents can have detrimental effects has been known for some time, because of the tendency of these agents to cause subsensitivity (tachyphylaxis). There is a slight reduction in peak bronchodilation and a more severe reduction in the duration of bronchodilation.[1,2] Tachyphylaxis occurs also in terms of the bronchoprotective effect of adrenergic agents. Thus, after 1 week of regular administration of terbutaline, there is a significant decrease in its ability to protect from challenges with both methacholine and adenosine monophosphate (AMP).[3]

The next discovery was that regular use of adrenergic agents can increase non-specific bronchial hyperreactivity.[4] This is probably not due to subsensitization.[5]

However, the most clinically relevant evidence came with the study by Sears and associates showing that regular administration of fenoterol, compared with 'as needed' use, caused not only an increase in bronchial hyperreactivity, but also worsened clinical control of asthma.[6]

Cockcroft and associates have demonstrated a worsening of the late allergic reaction and increase in non-specific bronchial reactivity that accompanies the late allergic reaction in the presence of regular use of albuterol (Fig. 1).[7] In a later study, it was shown that this is accompanied by an increased eosinophil influx into the airways.[8]

One possible explanation for the detrimental effect of regular use of albuterol is the fact that it is a racemic drug containing equal proportions of two isomers: R-albuterol, which causes the bronchodilator effect, and S-albuterol, which has pro-inflammatory actions.[9] Because there is disproportionate accumulation of S-albuterol during regular administration of racemic albuterol, the pro-inflammatory effect of S-albuterol may predominate.

In some epidemiologic studies, regular use of adrenergic agents has been associated with increased risk of death or near death from asthma.[10] A causal relationship cannot be established from these studies, because frequent use of these drugs could simply be a marker of more severe asthma. However, use of inhaled corticosteroids or oral corticosteroids, which are also markers of severe asthma, was not associated with increased risk of death.

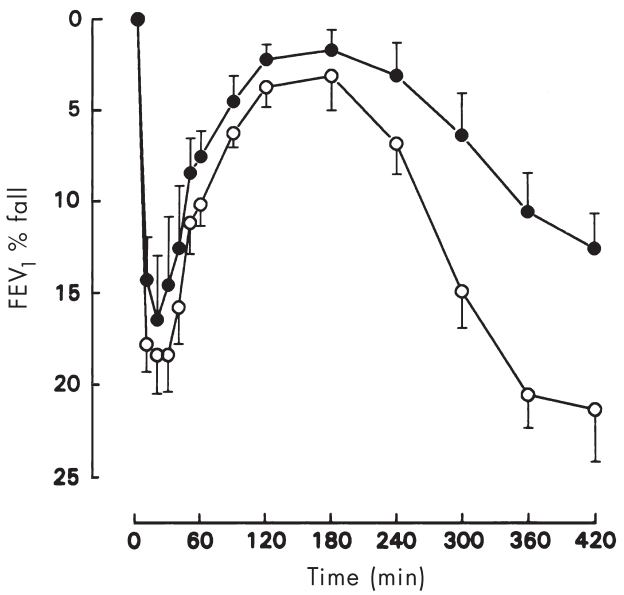

Fig. 1 Mean percent change in forced expiratory volume in 1 s (FEV_1) versus time for the allergen challenges after 1 week of placebo (●) and 1 week of albuterol 200 μg four times daily (○). From Cockroft DW, O'Byrne PM, Swystun VA, Bhagat R. Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J. Allergy Clin. Immunol.* 1995; **96**: 44–9, with permission.

One possible explanation for the association with increased risks of death from asthma is found in a study by Bel and associates.[11] They have shown that pretreatment with albuterol before a histamine or methacholine challenge test gives initial protection against the lower doses of these agents. However, when larger doses are reached, there is a very steep fall in forced expiratory volume in 1 s (FEV_1). If this occurs with naturally occurring triggers, it could explain a life-threatening bronchospastic event.

Not all studies that have compared regular versus 'as needed' use of adrenergic agents have shown worsened clinical control on regular use. In some studies, clinical control was equally good[12] or even slightly better on regular administration.[13–15] However, the total number of doses of adrenergic agents per day needed to give this degree of control was 2–3-fold greater in the regular regime than in the 'as needed' one; hardly a good argument for regular use.

It is clear that maintenance therapy with short-acting beta-adrenoreceptor agonists can have some detrimental effects and, considering their lack of anti-inflammatory effects, this type of treatment should be used only if very aggressive anti-inflammatory treatment fails to control the symptoms.

First-line anti-inflammatory drugs

Another major debate is whether inhaled corticosteroids or non-steroidal anti-inflammatory drugs, such as DSCG, should be used as first-line anti-inflammatory treatments.

The earlier asthma Guidelines[16] recommended the start of anti-inflammatory treatment in moderately severe patients, defined as having symptoms on more than 3 days per week. In children, these Guidelines recommended a step-wise approach, using DSCG first and switching to inhaled corticosteroids only if DSCG failed to control the disease. A study by Agertoft and Pedersen has questioned the step-wise approach and has suggested that delay in starting inhaled corticosteroids could cause irreversible airway obstruction.[17] Therefore, they suggest that inhaled corticosteroids should be the first-line anti-inflammatory therapy. However, in this study only prebronchodilator measurements of FEV_1 were shown, with no attempt to reverse the obstruction. Therefore the authors could not really comment whether the obstruction was reversible or not.[17]

My group has performed a study on the long-term outcome of childhood asthma,[18] in patients treated according to the International Pediatric Guidelines.[16] The follow-up period was 8.4 years (range 2–16 years), longer than the follow-up in the Agertoft and Pedersen study (3–5 years).[17]

The initial treatment was 'as needed' bronchodilators for mild patients, DSCG for moderately severe patients and inhaled corticosteroids for severe patients who could not be controlled by DSCG. The patients were followed regularly in the clinic and treatment was adjusted up, if they got worse, or down (step-down), if they were doing well. At the end of the follow up, approximately half of the patients treated with DSCG or inhaled corticosteroids improved, while only 17% of those treated with bronchodilators did so. We found that delay in starting DSCG had a detrimental effect on the clinical outcome, but delay in starting inhaled corticosteroids did not have any significant effect. Results from pulmonary function tests in the two groups treated with anti-inflammatory drugs (DSCG or inhaled corticosteroids) improved during the follow up, while they deteriorated in patients treated with bronchodilators (Fig. 2). Post-bronchodilator values in the group treated with DSCG, were the highest of the three groups and they were quite normal.

In patients treated with DSCG, there was no evidence that in the absence of treatment with inhaled steroids

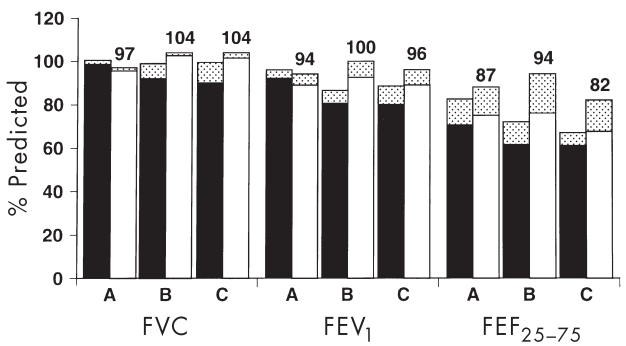

Fig. 2 Pulmonary function tests (forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), forced expiratory flow in the middle half of the FVC (FEF_{25-75}) at start (■) and end (□) of follow-up and after bronchodilator use at these time points (▨). Group A, initially treated with prn ('as needed') β-agonists. Group B, initially treated with sodium cromoglycate. Group C, initially treated with inhaled corticosteroids. Treatments at end of follow-up were changed from initial treatment in some patients. (Modified from König P. Evidence for benefits of early intervention with non-steroidal drugs in asthma. *Pediatr. Pulmonol*. 1997; Suppl. 15: 34–9. Copyright ©1997 Wiley-Liss Inc.).

irreversible airway obstruction occurs, as suggested by Agertoft and Pedersen.[17]

Our conclusions were that the step-wise approach starting with DSCG has a good long-term outcome, but the start of DSCG treatment should occur in milder patients than the recommendations of the First International Pediatric Guidelines[16] recommend (patients symptomatic more than 3 days/week).

A cross-sectional study of Finnish schoolchildren,[19] based on the same Guidelines,[16] has also concluded that the best pulmonary function tests are obtained in the moderately severe group treated with non-steroidal anti-inflammatory drugs (DSCG or nedocromil sodium) and that the start of treatment with these drugs should be earlier than the recommendations of those Guidelines.[16] A later set of Guidelines did indeed change these recommendations to starting non-steroidal anti-inflammatory drugs in patients symptomatic on more than 1 day per week (Global Initiative for Asthma, 1995[20]).

In deciding on the risk/benefit ratio, one would instinctively assume that, in terms of efficacy, inhaled corticosteroids are superior to DSCG. However, reviewing the pediatric literature shows that this superiority is only clear-cut in studies where the patients had severe asthma,[21–23] while in patients with mild-to-moderate disease, three of five studies showed equal efficacy[24–26] and only two studies[27,28] showed superior results with inhaled corticosteroids.

In terms of safety, DSCG has an excellent record.[29] Although inhaled corticosteroids have far fewer side-effects than systemic corticosteroids, their safety record is not as good as that of DSCG. In addition to topical side-effects, such as oral candidiasis, dysphonia and cough,[30] inhaled corticosteroids can also have systemic side-effects, some even at regular doses.

Regular doses of beclomethasone dipropionate (approximately 400 μg/day) have been shown in numerous early studies,[31] mine included,[32] not to suppress growth. However, several later studies, with the same dose of beclomethasone dipropionate have shown significant growth suppression (Fig. 3).[33–36]

The most likely explanation of the difference between the early studies showing no growth suppression and the more recent studies that do show suppression with the same dose is that the early studies were done on severe patients, while the more recent studies examined mild-to-moderate patients. There are several reasons why the severity of the disease can have an effect on the systemic side-effects of inhaled corticosteroids. Generally,

severe patients have more severe airway obstruction and therefore less of the inhaled drug penetrates to the lung and becomes bioavailable through the lungs. This has been demonstrated in adults treated with fluticasone (2 mg/day), which caused greater adrenal suppression in mild patients than in severe patients.[37]

Specifically regarding growth suppression, in severe patients inhaled corticosteroids can have two beneficial effects on growth. First, severe patients often need short and more prolonged courses of systemic steroids, which have a more potent growth suppressive effect than inhaled corticosteroids. When these patients are treated with inhaled corticosteroids, the need for systemic steroids disappears or greatly decreases. Second, poorly controlled asthma in itself can cause growth suppression.[38] Treatment with inhaled corticosteroids will greatly improve control of asthma, therefore improving growth. Thus, these two beneficial effects cancel out the negative effect on growth and no growth suppression results. In mild patients, there is usually no need for systemic steroids and although control of asthma improves with addition of inhaled corticosteroids, the improvement is not as dramatic as in severe patients. Thus, the beneficial effects of inhaled corticosteroids are absent or weaker and the negative effect predominates, resulting in growth suppression (Fig. 4).

Recently, the US Food and Drug Administration (FDA) has requested the manufacturers of inhaled and nasal corticosteroids to include a warning that they may slow growth rates in children. The FDA has requested labeling that clinical studies found a mean 'growth velocity' reduction of about 1 cm per year (range 0.3–1.8 cm per year) and that the effect appears to be related to dose as well as duration.

The fact that inhaled corticosteroids cause more systemic side effects in milder patients is an important consideration, because one should be less tolerant of side effects in mild patients than in severe ones.

Another systemic side effect with regular doses of inhaled corticosteroids (400 μg beclomethasone dipropionate) is adrenal suppression, especially at night.[39] However, the clinical significance of this statistically significant adrenal suppression is not clear, because these patients do not develop life-threatening adrenal insufficiency.

A side effect shown with regular doses of budesonide (400 μg/day) in adults is decreased skin collagen synthesis.[40]

In adults treated with large doses of inhaled corticosteroids, purpura and skin thinning have been described.[41,42]

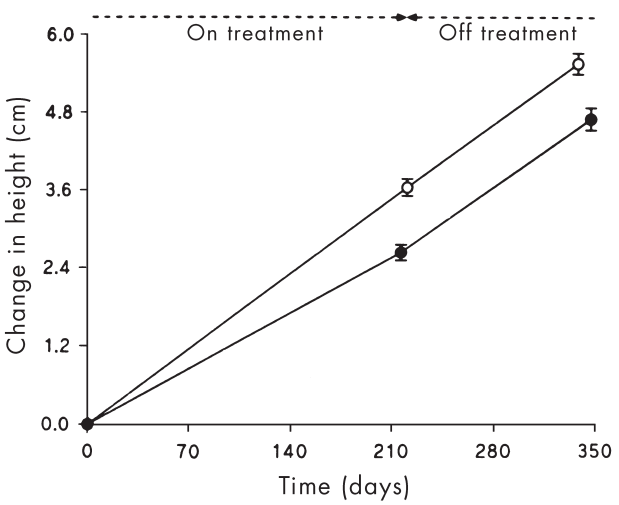

Fig. 3 Change in height from baseline of children receiving beclomethasone dipropionate (●) and those receiving placebo (○). (From Doull IJM, Freezer MJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am. J. Respir. Crit. Care Med.* 1995; **151**: 1715–19, with permission).

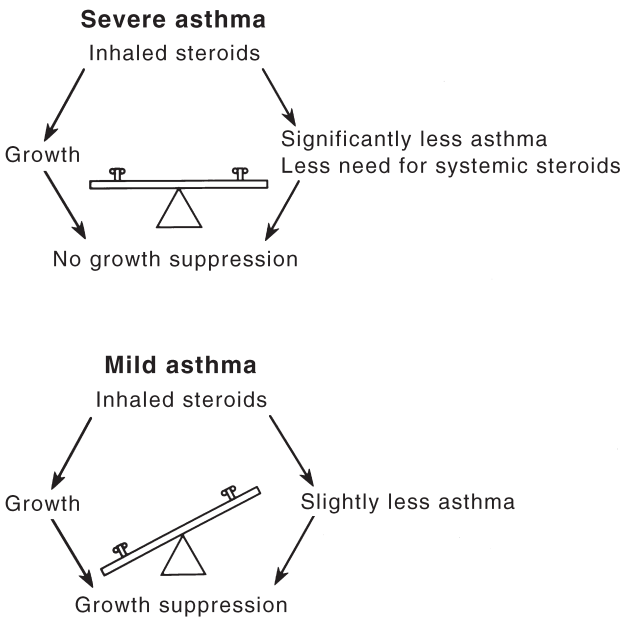

Fig. 4 Growth suppression with inhaled corticosteroids in severe versus mild asthma. (From König P. Evidence for benefits of early intervention with non-steroidal drugs in asthma. *Pediatr. Pulmonol.* 1997; Suppl. 15: 34–9. Copyright ©1997 Wiley-Liss Inc.

Theoretically, there is also the possibility that corticosteroids could increase IgE synthesis. This has been shown with oral administration[43] and skin application[44] of corticosteroids, but it has not been studied with inhaled corticosteroids. Interestingly, in a Japanese study, DSCG has been shown *in vitro* to decrease IgE production.[45]

A note of caution that needs to be remembered for inhaled corticosteroids is that, in addition to dose and specific properties of each drug, the delivery system will also have an effect on systemic bioavailability and therefore systemic side-effects. Thorsson and associates have compared the same dose of budesonide (400 μg) by two delivery systems: metered-dose inhaler (MDI) and dry powder inhaler.[46] The lung deposition with the dry powder was about double compared with the MDI, increasing the total systemic bioavailability by about 50%. Because of the detrimental effect on the ozone layer, MDI driven by chlorofluorocarbons (CFC)-based propellants are being phased out all over the world. All inhaled corticosteroids are being switched to either powder inhalers or MDI using hydrofluoroalkane (HFA). Delivery to the lungs using these systems can be very different (in most cases increased) from the CFC-driven MDI and therefore everything that was learned about both efficacy and safety of inhaled corticosteroids needs to be studied again. One cannot assume that the same drug, in the same dose, will have the same safety profile as with the older delivery systems.

In conclusion, because of comparable efficacy in the milder patients and better safety, DSCG is better suited for first-line anti-inflammatory treatment than inhaled corticosteroids and a step-wise approach, starting with DSCG and switching to inhaled corticosteroids only if this fails, as recommended by the Guidelines,[16,20,46] is still the logical approach.

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